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WO 2004/016595 A1

(54) Title: METHOD FOR THE SELECTIVE PREPARATION OF 3-OXO-4-AZA-5A-ANDROSTANE COMPOUND

(57) Abstract: This invention relates to a method for selectively preparing the 3-oxo-4-aza-5¥á-androstane compound which is used as an intermediate of finasteride by heating 3-oxo-4-aza-5-androstene in a mixture of formic acid and an alkanediol in the presence of zinc.

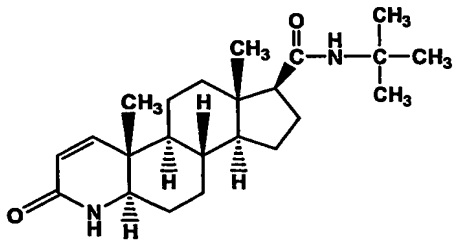
METHOD FOR THE SELECTIVE PREPARATION OF 3-OXO-4-AZA-5α-ANDROSTANE COMPOUND

FIELD OF THE INVENTION

The present invention relates to an improved method for selectively preparing 3-oxo-4-aza-5α-androstane compound under mild conditions.

DESCRIPTION OF THE PRIOR ART

Finasteride (17β-(N-tert-butylcarbamoyl)-5α-4-aza-androst-1-en-3-on), the compound of formula (II) having an androstane backbone, is effective in treating benign prostatic hypertrophy and androgenetic alopecia:

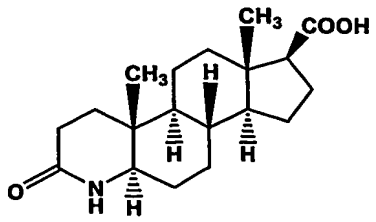


(II)

Benign prostatic hypertrophy and androgenetic alopecia are caused by binding of 5α-dihydrotestosterone (DHT) derived from testosterone to androgen receptor. The conversion of testosterone into 5α-dihydrotestosterone is mediated by testosterone 5α-reductase which is inhibited by finasteride. Such inhibition of 5α-dihydrotestosterone by finasteride results in rapid recovery of prostate and increased hair growth. Finasteride thus is effective to benign prostatic hypertrophy and good agent for treating androgenic alopecia which exhibits only low, temporary side effects, and it is the only orally administrable among the two hair-growth agents approved by FDA of the United Sates.

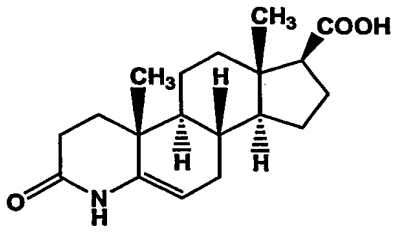
Finasteride can be conventionally prepared by converting the carboxylic group of the 17β-position of 3-oxo-4-aza-5α-androstane-17β-carboxylic acid of formula (I) into a t-butylcarbamoyl group and then carrying out dehydrogenation at the 1,2-positions, or carrying out dehydrogenation at the

1,2-positions and then converting the 17β-position carboxylic group into a t-butylcarbamoyl group:



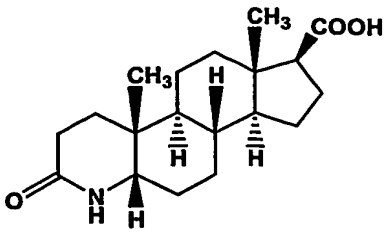
(I)

For example, a process for preparing 3-oxo-4-aza-5α-androstane-17β-carboxylic acid of formula (I) is disclosed in U.S. Patent No. 4,760,071 and the *J. Med. Chem. 29, 2298 (1986)*, wherein the 3-oxo-4-aza-5-androstene compound of formula (III) is reduced with the hydrogen in the presence of a PtO_2 catalyst under a hydrogen atmosphere of 40psi to produce the compound of formula (I).



(III)

The above reduction process selectively produces the compound of formula (I) having the 5-hydrogen oriented at 5α-position, without giving the isomer thereof, the compound of formula (IV) having the 5-hydrogen at the 5β-position. However, this asymmetric reduction process requires the use of explosive hydrogen and an expensive catalyst under high pressure condition.



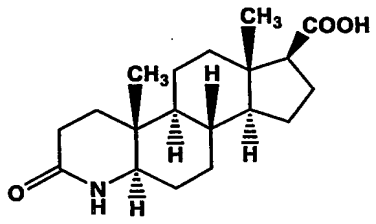
(IV)

Also disclosed in *J. of Pharmaceutical Sciences. 63, p 19 (1974)* is a method of reducing a steroid compound having a structure similar to the compound of formula (III) to produce a 5α-compound using formic acid and N-methylformamide. However, this process is conducted under high temperature and high pressure conditions and gives a poor productivity.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the present invention to provide an improved method for selectively preparing the compound of formula (I) under mild conditions.

In accordance with the present invention, there is provided a method for preparing the compound of formula (I) comprising heating the compound of formula (III) in a mixture of formic acid and an alkanediol in the presence of zinc:



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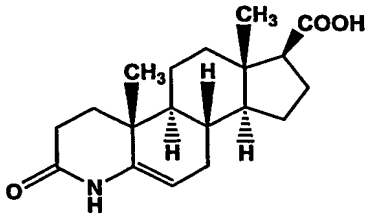


(III)

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the following accompanying drawings, which respectively

show:

FIG. 1: a high performance liquid chromatography (HPLC) scan of the compound of formula (I) prepared in accordance with the inventive method; and

FIG. 2: an HPLC scan of the compound of formula (I) prepared in Comparative Example 1 in the absence of zinc; and

FIG. 3: an HPLC scan of the compound of formula (I) prepared in Comparative Example 2 using formic acid and methylformamide.

DETAILED DESCRIPTION OF THE INVENTION

The compound of formula (III) used as a starting material of the present invention can be prepared by a conventional method (U.S. Patent No. 4,760,071 and the *J. Med. Chem. 29, 2298 (1986)*).

In accordance with the present invention, the compound of formula (I) can be prepared by dissolving the compound of formula (III) in a mixture of formic acid and an alkanediol, adding activated zinc thereto, and heating the resulting mixture.

In the inventive method, formic acid may be used in an amount of 3 to 30ml, preferably 5 to 15ml based on 1.0g of the compound of formula (III); and the alkanediol, in an amount of 2 to 20ml, preferably 5 to 10ml, based on 1.0g of the compound of formula (III).

The alkanediol which may be used in the present invention includes ethylene glycol, propylene glycol, 1,3-propanediol, 1,2-butanediol, 1,3-butanediol, 1,4-butanediol and 2,3-butandiol, and the like, among which ethylene glycol is preferred.

The zinc used in the present invention enhances both the selectivity of the target 5α-compound and the yield, and also reduces the reaction time. Zinc may used in 4 to 10 equivalents, preferably, 6 to 8 equivalents, based on a mole of the compound of formula (III), and in the total absence of the isomeric 5β-byproduct, the target 5α-compound is produced in a high yield of 80%. When zinc is not used, the target 5α-compound is produced in a yield of only about 50% together with 10 to 20% of the isomeric 5β-compound.

The reduction in accordance with the present invention may be carried out at a temperature of 80 to 130℃, preferably 100 to 110℃, for 4 to 8 hours.

Thus, in accordance with the simple method of the present invention,

the target compound of formula (I) can be selectively produced in a high yield under mild conditions.

The present invention will be described in further detail with reference to Examples. However, it should be understood that the present is not restricted by the specific Examples.

Example

Preparation 1: Preparation of 17β-carboxy-5-oxo-A-nor-3,5-secoandrostan-3-onic acid

16g (50mmol) of 3-oxo-4-androstene-17β-carboxylic acid was dissolved in 240ml of t-butanol, 16g (150mmol) of sodium carbonate dissolved in 40ml of water was added thereto, and then heated to 80℃. Added dropwise thereto was a solution, which is preheated to 60℃, of 53.5g (250mmol) of sodium metaperiodate and 4.0g (25mmol) of potassium permanganate dissolved in 300ml of water. The resulting mixture was refluxed for 3 hours and left at room temperature overnight. The inorganic materials were filtered-off through celite, the filtrate was successively washed with water and 250ml of 10% sodium hydrogen sulfite, t-butanol was removed under a reduced pressure, and the residue was acidified with concentrated HCl. The acidified residue was then extracted with 320ml of methylene chloride, washed successively with 320ml of 5% sodium hydrogen sulfite and 320ml of brine, and distilled under a reduced pressure, to obtain 14.5g of the title compound (yield: 86%) as a pale yellow solid.

H-NMR(δ , $CDCl_3$): 0.82(3H, 19-CH_3), 1.16(3H, 18-CH_3), 1.20~2.30 (15H, cyclic-CH), 1.53(2H, 1-CH_2), 2.40(2H, 2-CH_2), 2.50(1H, 17-CH), 11.85(1H, COOH)

Preparation 2: Preparation of 3-oxo-4-aza-5-androstene-17β-carboxylic acid (the compound of formula (III))

10g of 17β-carboxy-5-oxo-A-nor-3,5-secoandrostan-3-onic acid (30mmol) obtained in Preparation 1 was dissolved in 30ml of ethylene glycol, and 75ml of 2.0M ethanolic ammonia solution (150mmol) was added thereto,

stirred for an hour at 40 to 50℃, and refluxed for 12 hours. The resulting mixture was cooled to room temperature and ethanol was distilled off under a reduced pressure. To the residue was added 150ml of water and the resulting mixture was acidified with 10% HCl to pH 1.5. Precipiates formed were filtered, washed with water, and dried at 45℃, to obtain 6.6g of the title compound (yield: 70%) as a white solid.

H-NMR(δ , DMSO-d_6): 0.57(3H, 19-CH_3), 0.91(3H, 18-CH_3), 0.95~2.30 (18H, cyclic-CH), 4.76(1H, 6-CH), 9.17(1H, NH), 11.85(1H, COOH)

Example 1: 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (the compound of formula (I) - 1)

3.2g (10mmol) of 3-oxo-4-aza-5-androstene-17β-carboxylic acid obtained in Preparation 2 was dissolved in a mixture of 45ml of formic acid and 15ml of ethylene glycol, and 2.6g (80mmol) of activated zinc was added thereto. The mixture was reacted for 8 hours at 100 to 105℃ and cooled to room temperature. The suspended solid was removed by filteration, and the solvent in the filtrate was removed under a reduced pressure. 13ml of N-methylformamide was added to the residue, and the resulting mixture was stirred for 30 minutes in an ice bath. Precipitates formed were then filtered and dried at 45℃, to obtain 2.6g of the title compound (yield: 81%) as a white solid.

The product thus obtained was analyzed by HPLC and the result is shown in FIG. 1. As can be seen in FIG. 1, only the target 5α-compound (retention time: 11.996) is detected, the isomeric 5β-compound being not detectable.

H-NMR(δ , DMSO-d_6): 0.56(3H, 19-CH_3), 0.72(3H, 18-CH_3), 0.80~1.30 (8H, cyclic-CH), 1.40~1.70(7H, cyclic-CH), 1.87(2H, 16-CH), 2.10(2H, 2-CH_2), 2.30(1H, 17-CH), 3.0(1H, 5-CH), 7.15(1H, NH), 11.85(1H, COOH)

Example 2: 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (the compound of formula (I) - 2)

3.2g (10mmol) of 3-oxo-4-aza-5-androstene-17β-carboxylic acid

obtained in Preparation 2 was dissolved in a mixture of 16ml of formic acid and 32ml of ethylene glycol, and 2.6g (80mmol) of activated zinc was added thereto. The mixture was reacted for 8 hours at 110 to 120℃, and cooled to room temperature. The suspended solid was removed by filtration, formic acid was removed under a reduced pressure. The residue was dissolved in 300ml of chloroform and washed successively with 150ml portions of 5% aqueous sodium carbonate solution (x2) and 150ml portions of water (x3). The chloroform layer was separated, then dried, filtered and the solvent was removed under a reduced pressure. 13ml of N-methylformamide was added to the residue and stirred for 30 minutes in an ice bath. Precipitates formed were then filtered and dried at 45℃, to obtain 2.7g of the title compound (yield: 83%) as a white solid.

The product thus obtained was analyzed by HPLC and the result showed that only the 5α-compound (retention time: 11.996) was produced. H-NMR data was the same as in Example 1.

Comparative example 1: Preparation of 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (the compound of formula (I)) in the absence of zinc

3.2g (10mmol) of 3-oxo-4-aza-5-androstene-17β-carboxylic acid obtained in Preparation 2 was dissolved in a mixture of 45ml of formic acid and 15ml of ethylene glycol, and reacted for 8 hours at 100 to 105℃. The reaction mixture was cooled to room temperature, the residual solid was remove by filtration and the solvent was distilled off under a reduced pressure. 13ml of N-methylformamide was added to the resulting residue and stirred for 30 minutes in an ice bath. Precipitates formed were then filtered and dried at 45℃, to obtain 1.7g of the title compound (yield: 53%) as a white solid.

The product thus obtained was analyzed by HPLC and the result is shown in FIG. 2, wherein the ares of 5β-compound peak (retention time: 12.956) is 15% relative to the area of the 5α-compound peak (retention time: 12.187) of 85%. That is, a large amount of the undesired 5β-compound is produced.

Comparative example 2: Preparation of 3-oxo-4-aza-5α-androstane-17β-

carboxylic acid (the compound of formula (I)) using a mixture of formic acid and N-methylformamide

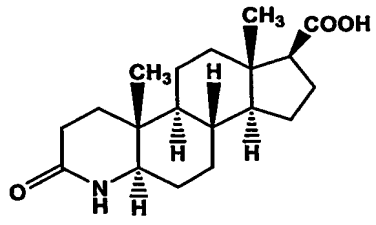
3.2g (10mmol) of 3-oxo-4-aza-5-androstene-17β-carboxylic acid obtained in Preparation 2 was dissolved in a mixture of 45ml of formic acid and 15ml of N-methylformamide, and reacted for 8 hours at 100 to 105℃. The reaction mixture was cooled to room temperature, the residual solid was filtered off, formic acid was removed under a reduced pressure, and the remaining solution was stirred for 30 minutes in an ice bath. Precipitates formed were then filtered and dried at 45℃, to obtain 1.9g of the target compound (yield: 59%) as a white solid.

The product thus obtained was analyzed by HPLC and the result is shown in FIG. 3, wherein the area of the 5β-compound peak (retention time: 12.770) is 35% relative to the 5α-compound peak (retention time: 12.046) of 65%. That is, a large amount of the undesired 5β-compound is produced.

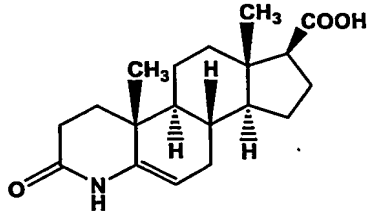
While the invention has been described with respect to the specific embodiments, it should be recognized that various modifications and changes may be made by those skilled in the art to the invention which also fall within the scope of the invention as defined as the appended claims.

WHAT IS CLAIMED IS:

1. A method for preparing the compound of formula (I) comprising heating the compound of formula (III) in a mixture of formic acid and an alkanediol in the presence of zinc:



(I)



(III)

2. The method of claim 1, wherein formic acid is used in an amount of 3 to 30ml based on 1.0g of the compound of formula (III).

3 The method of claim 1, wherein the alkanediol is selected from the group consisting of ethylene glycol, propylene glycol, 1,3-propanediol, 1,2-butanediol, 1,3-butanediol, 1,4-butanediol and 2,3-butandiol.

4. The method of claim 1, wherein the alkanediol is used in an amount of 2 to 20ml based on 1.0g of the compound of formula (III).

5. The method of claim 1, wherein zinc is used in 4 to 10 equivalents based on a mole of the compound of formula (III).

6. The method of claim 1, wherein the heating is carried out for 4 to 8 hours at a temperature in the range of 80 to 130℃.

FIG. 1

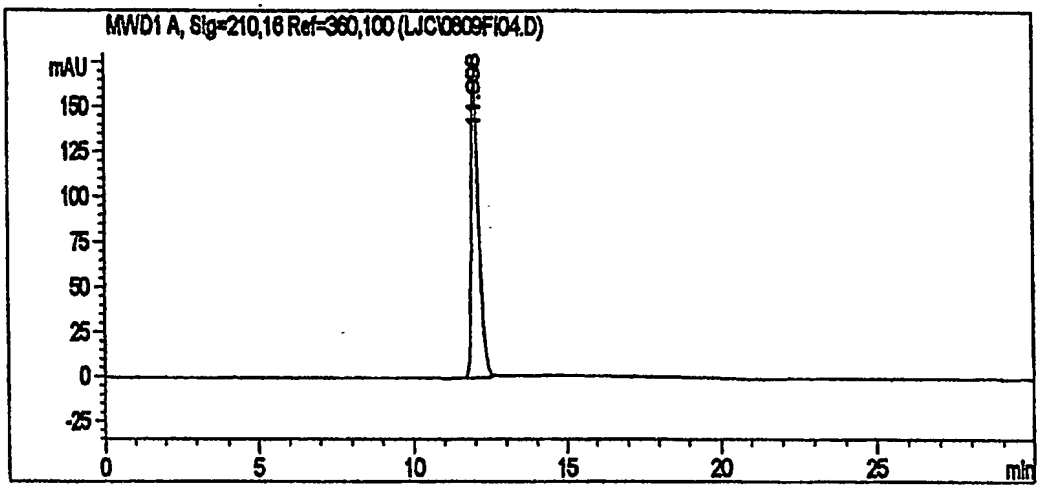

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FIG. 2

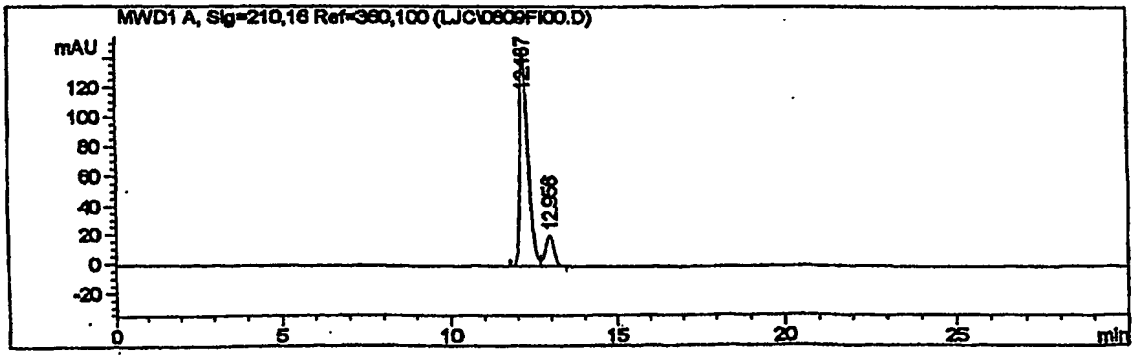
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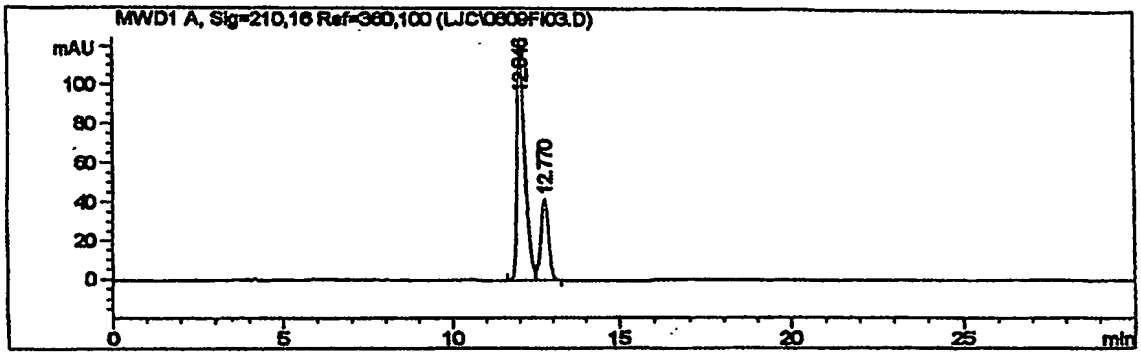
FIG. 3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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/01629

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 221/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 221/18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN online, CA on CD, KIPASS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/46207 A2 (Glaxo group limited) 13 June 2002 (2002-06-13) page7, line 7-30 example 1-2	1-6
A	US 5804576 A (Research Corporation Technologies, Inc.) 8 September 1998 (1998-09-08) scheme 1 section 37, line 49-50	1-6
A	US 4451405 A (Glaxo group limited) 29 May 1984 (1984-05-29) section 5, line 63-65	1-6
A	John F. Templeton, Samar Majid, and Angelina Marr, 'Zinc-Acetic Acid Reduction of the Steroid 4-En-3-one: Novel Conversion of the 4-En-3-one into the 2-En-4-one via a Vinyl Chloride, J. Chem. Soc. Perkin Trans. 1, 1990, Vol.9, p.2581-2584 page 2581 left column line 8-18; claim 1 page 2582 Experimental section 2a; claim 1	1
A	Peng Xia et al., 'Synthesis of N-substituted 3-Oxo-17beta-carboxamide-4-aza-5alpha-androstanes and the Tautomersim of 3-Oxo-4-aza-5-androstenes', Heterocycles, 1998, Vol.47(2), p.703-716 page 704, line 8-20; claim 1 page 705, line 12-page 706, line 2; claim 1	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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25 NOVEMBER 2003 (25.11.2003)	26 NOVEMBER 2003 (26.11.2003)

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LEE, HYUN SONG
Telephone No. 82-42-481-5606

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/01629

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO0246207A2	13.06.2002	WO0246207A3	2003-03-20
		NO20031995A0	02.05.2003
		GB0026876A0	20.12.2000
		EP1335930A2	20.08.2003
		CA2427709AA	13.06.2002
		AU0241624A5	18.06.2002
US5804576A	08.09.1998	US5804576A	08.09.1998
US4451405A	29.05.1984	AU8095782A	09.09.1982
		EP0059637A1	08.09.1982
		GB2093846A	08.09.1982
		JP57158800A	30.09.1982
		NZ199859A	19.10.1984
		US4451405A	29.05.1984
		ZA8201337A	23.02.1983